Drug and Therapeutics Committee Training Course

Session 3: Assessing Drug Efficacy

Participant's Guide

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PURPOSE AND CONTENT

This session is intended to provide the participants with a basic guide on how to determine drug efficacy, primarily through review of the drug literature. Systematic and thorough evaluations of the drug literature will provide the Drug and Therapeutics Committee (DTC) with unbiased information necessary to select appropriate drugs for the formulary.

In most countries, evaluating the literature is commonly done by physicians and pharmacists. Unfortunately, it is often done incorrectly. With the tools presented in this session and practice at home, practitioners will be better equipped to evaluate the literature on a systematic and scientific basis.

Objectives

After completion of this session, participants will be able to—

- Understand the importance of determining efficacy and evaluating the clinical literature
- Discuss the different types of drug study design
- Describe the key components to review in a drug article
- Understand basic data interpretation techniques for drug studies
- Discuss the use of meta-analysis in the evaluation of the clinical literature

Preparation

Read Participant's Guide.

Further Readings

Cho, MK and Bero, L. Instruments for assessing the quality of drugs studies published in the medical literature. *JAMA* July 13, 1999;272(2):101–4.

Fowkes, FGR and Fulton, PM. Critical appraisal of published research: introductory guidelines. *BMJ* 1991;302:1136–40.

Gehlbach, SH. *Interpreting the Medical Literature.* Third edition. New York: McGraw-Hill, Inc. 1993.

Management Sciences for Health. *Managing Drug Supply.* Second edition. Chapter 30, "Drug and Therapeutics Information." West Hartford, CT: Kumarian Press. 1997.

INTRODUCTION

There has been an incredible increase in the number of drugs marketed over the past 20 years. This number is increasing even faster in this decade as drug companies rush to satisfy the world's desire for medical therapies. There are more than 100,000 pharmaceutical preparations on the world market today. Drug manufacturers research and develop drugs not only for the ultimate goal of treating and preventing disease, but also for the high profits that are available in this line of business. Business is booming.

In order to make available to the hospital a reasonable number of drugs that are effective, safe, of desirable quality, and of reasonable cost, the DTC must take meaningful steps to screen drugs and select the best available. This requires methodically evaluating the literature to make informed decisions on the efficacy and usefulness of each drug.

There are very few pharmacists or physicians who take the time or have the skills necessary to accurately evaluate a journal article describing a drug study. They frequently read the abstract and conclusions with little or no attention to the structure and validity of the written article. Thus, they may fail to recognize articles based on poorly designed studies with inaccurate or invalid conclusions.

This session discusses the basic information the DTC needs to evaluate the drug literature. Analyzing an article takes time and skill, but with training and practical experience this important task will become easier and extremely valuable.

IMPORTANT ELEMENTS OF AN ARTICLE

The primary literature is the most important source for unbiased information concerning any new drugs to be added to the formulary. It is here that you can find details about the research that was accomplished and how conclusions were formed concerning the drugs that were studied. The article itself can be described as having six distinct sections.

Abstract

The abstract provides a succinct summary of the drug study including objectives, methodology, results, and conclusions. The abstract must clearly state the objective of the drug study that follows. From this abstract, you should be able tell if the article is of value in your drug evaluation needs.

Introduction

This is the first section of the article and provides background and preface information for the reader. There should be a discussion of drugs used, disease states treated, review of other similar studies, and clearly stated, precise objectives.

Methodology

This section states how the study is conducted, including the design, selection criteria (for sample and for controls), and methodology to collect and analyze all data in the article. Inclusion and exclusion criteria should be described thoroughly. The method of matching randomization and blinding techniques used in the clinical study should be discussed in detail. Statistical methods used in all facets of the study must be described in detail.

Details about any drug treatments should be discussed here, including drugs used, dosing regimens, and length of time for treatments.

Results

The results section provides the actual outcomes of the study. This section often includes graphical presentation as well as written results. The results section should account for all patients who entered the study, making sure to identify those who did not complete the study and describing the reasons for noncompletion (including deaths). Reasons for any missing data should be presented in this section. Results should pertain only to this study and not to other similar studies.

Discussion and Conclusions

This section provides a discussion of the findings of the study and comments on their significance. The importance of limitations and strengths should be pointed out and a concise conclusion that is based solely on results of the study should be presented. Patient compliance with study parameters should also be discussed, especially compliance with drug regimens. Also, any distorting factors need to be discussed, including confounders and contamination that may have an effect on the results of the study

References

The reference section provides acknowledgment of references used in providing information in the article. It also gives readers the opportunity to identify other related articles and texts.

Acknowledgement

The acknowledgement section provides information on important contributors to the study, including funding sources. This section may be useful to identify any pharmaceutical company funding or support that may indicate a conflict of interest.

IMPORTANT CONCEPTS ABOUT CLINICAL STUDIES

This section discusses basic research terminology needed for the reader to understand how to evaluate clinical drug trials, also known as intervention studies. Readers are encouraged to see the key reading section of this Participant's Guide to obtain more detailed information concerning this subject.

Basic Drug Study Design

There are three fundamental types of drug study design—experimental, observational, and descriptive.

- Experimental studies evaluate the efficacy of drug therapy and other therapeutic modalities. These studies include the common study designs such as clinical trials, the type of study where most drug comparisons take place. The randomized controlled trial is the most important type of experimental study used and provides the most reliable results. It is considered the "gold standard" of experimental studies. This is the best type of study from which to draw conclusions on effectiveness of treatments. Randomized controlled trials are important because this is the only study design that will control for bias and many confounding variables and ultimately provide the most accurate and reliable results. However, randomized controlled trials are expensive and time-consuming, and can raise ethical concerns about the treatment strategies. Therefore, many investigators may select not to use this type of study design

- Observational studies are used for detecting causes of health care problems. Examples of these studies include case control (including retrospective), cohort, and cross-sectional studies. These studies do not control for all of the variables inherent in a study and, thus, they may not have the same importance as a randomized control study.

  The retrospective drug study is an example of an observational study design. This common type of study provides good information about drug effectiveness, but it is not as accurate and predictive as the prospective trial. Retrospective trials are conducted frequently because they are easier to do, cost less money, and do not impose ethical questions about subjecting a patient to therapies that may not work or may be harmful. Researchers wanting to examine the effects of antihypertensive drugs on the prevention of stroke would have to wait decades before obtaining enough information in a prospective trial. Retrospectively, one can look back over several decades and observe

the effects of these drugs on the incidence of stroke. These studies are valuable, but they have design flaws that make them difficult to interpret.

In a cohort study, groups of patients with similar inclusion and exclusion criteria are followed prospectively. Cohort studies are frequently used to identify risk factors for disease states or unknown adverse drug reactions to new drugs.

- Descriptive studies use case reports and clinical series reports to describe information from a study. An example of this is a report of a serious adverse side effect attributed to an antimicrobial drug used to treat pneumonia. Another example would be a study that looks at the incidence of community-acquired pneumonia in children.

The following are some key components of a clinical trial that participants in this session should become familiar with in order to evaluate the clinical literature.

Sampling

Sampling is the term used to describe the selection of patients for a clinical study. When most clinical studies are done, they should aim to obtain a small cross-section of the population, one that represents different ages, ethnicity, regions of the country, life styles, and health conditions. In some types of studies, the sampling will be more targeted and look at a particular population group or health condition.

Choosing a sample is complex and involves well-designed criteria in order for the sample to be highly representative of the population, i.e., it should be representative and relevant to the wider population to whom the research might apply. This is a critical step in any clinical study as poor selection criteria will result in a sample that is not representative of the general population and will produce errors in the statistical analysis.

There are two types of criteria that are commonly used to define the sample, inclusion and exclusion. The inclusion criteria describe the characteristics of subjects who are selected to enter the study, while exclusion criteria provide information on those subjects who have been rejected. This information will help the reader of the article determine the representativity of the population study group in relation to the one he or she is dealing with.

Sample size is critical to the study from the outset and must be large enough to detect a difference between the outcome measures of the study. The authors should state how the sample size was calculated.

Randomization

Randomization is a critical step in the early stages of a clinical trial. This involves the random selection of patients for entry into the study as well as the random selection of patients for a certain treatment modality during the study. True random selection occurs when patients are

selected by chance from a population and all of these patients have an equal opportunity of being assigned for the study.

Since only a few patients from a sample of larger patients will be chosen to participate in a study, randomization is critical to reflect the larger patient population for each study group. If randomization of patients is not effective, the results of the study will not truly represent the effects of the drug when it is used on the general population.

Clinical studies done in the 1970s and early 1980s were frequently conducted with poor randomization procedures. Results from these studies were generally accepted, but were not confirmed by better-designed randomized studies in later years. Clinical outcomes result from many causes, and a specific treatment modality is just one of those causes. Underlying disease processes, the presence of other diseases, and a host of other known and unknown factors often overwhelm any effect of treatment. Nonrandomized treatments offer only limited results that need to be interpreted with reference to possible bias, confounding, and lack of representatives from the general population.

Confounding Factors

A confounding factor or variable is one that affects the outcome of a study and therefore makes it difficult to determine the actual effects produced by the study drug. Confounders can also be described as an alternative explanation for a result in the study. There are many different factors in a study that have the opportunity to influence the intended study drug or therapeutic intent. For example, a study has shown that Drug A has been found to be effective for treating depression. A confounding factor would be that patients in the study group were also taking the herbal product St. John's Wort, known to have a role in affecting depression. The measured effect on depression may have been due to St. John's Wort rather than the study drug.

Control Groups

Comparative trials utilize control groups so that a comparison may be made between treatment modalities and patients who receive a different treatment or no treatment. Examples of control groups include placebo, alternative treatment, and historical. Control groups, like the sample group, must also be representative of the general population. The use of control groups provides the study with the ability to compare and evaluate the results with other studies using similar medications.

The assumption is that if the target population is truly chosen randomly there will be no differences between the intervention and control groups (placebo or nonintervention groups) and therefore that any observed difference will be due to the intervention alone.

Blinding

An experiment is "blinded" if the investigator and/or the patient is not aware of which experimental group the patient is participating in. Blinding certain parts of the study will prevent many types of bias from being introduced into the clinical trial.

Patients who know what treatment group they are in are very likely to have an opinion about that treatment's efficacy. This is also true of the investigator. These opinions or biases may distort the reporting of treatment outcomes and consequently distort the results.

Single-blinded studies are used to blind only one participant in the study, either the investigator or the study participants. In double-blinded studies, the investigator and the participants are blinded so that neither is aware of the treatment modality. This is the most desirable method to conduct the study, but it is expensive and cumbersome to carry out. Unintentional "unblinding" of the study can occur easily if patients and investigators become aware that a certain drug is being used because of an obvious therapeutic effect, significant side effects, a particular odor of the study drug, taste, or other clues.

Open label drug studies are not blinded to either party. These studies do not prevent bias that will inevitably occur. The investigator decides whether blinding may be unethical, not practical, or unnecessary.

Bias

Bias is the condition, either conscious or subconscious, that allows for systematic error to enter a clinical trial and leads to an incorrect estimate of the outcome of interest. A bias can be a prejudice or a specific opinion favoring an issue before there is adequate information to support the position. Different types of bias occur in all studies and careful design, blinding, and randomization will effectively limit bias. The two major types of bias are selection bias and measurement bias.

An example of selection bias would be an investigator who selects only those patients with relatively mild symptoms of asthma in a study to assess the efficacy of a drug. By doing so, the investigator can show improvement in a larger number of patients. The random selection of patients with asthma should include an appropriate number of patients with more severe symptoms, thus subjecting the study to more real-life conditions and more reliable results.

TESTING FOR STATISTICAL SIGNIFICANCE IN A STUDY

A clinical trial is always done from a small sample of patients and then extrapolated to the larger general population. When investigators extrapolate this information to a larger group or population, they use statistical inference. This inference is, strictly speaking, a generalization made about a large population drawn from information about a much smaller study population.

Null Hypothesis

In all scientific drug studies there is a hypothesis to be tested, one that says a drug is superior or safer or different due to some other parameter. There is also an opposing hypothesis, referred to as the null hypothesis, and if it is correct the study will show no difference between the two study groups. If the null hypothesis is not substantiated, and there is a difference between the two study groups, the investigator must only determine the significance of that difference. The difference may be a result of error inherent in the study or may be due to chance.

P Values and Statistical Significance

Typically, the null hypothesis says there is no difference between groups. If you reject it (at a certain level of significance), you are saying there is a difference. A Type I (alpha) error occurs when the null hypothesis is rejected when it is actually true. In every clinical study, when statistical significance is reached there needs to be an estimate of the probability that this significance has been reached by chance alone. This is referred to as the *p* value. When a study is said to have statistical significance, then it is unlikely to be due to chance if the *p* value is less than 5 percent (0.05). Ultimately, what this is saying is that there is less than 1 chance in 20 that the results of the study can be attributed to chance.

This value is not applicable to all studies, but it does represent the majority of studies concerning drug comparisons. A study that has a low *p* value does not necessarily reflect the significance of the study overall. It only shows that the chance of error being reflected in the final result is extremely low.

Statistical significance does not necessarily equal clinical significance. This is an important distinction. For example, a clinical study may show that a drug lowers blood glucose levels when compared to placebo by 20mg/dl. This may be statistically significant because of the study design and the large number of patients in the clinical trial, but it has little clinical significance because this amount of decrease in blood sugar would not be important (or clinically significant) in most diabetic patients.

Statistical Power

A Type II (beta) error is the probability of accepting the null hypothesis (that there is no difference) incorrectly. This type of error is less prominent and is also reflected in the number of subjects selected for the study. Statistical power is the complement of beta error (power = 1-beta error) and is described as the ability to detect a difference of a certain size between groups when a difference actually exists. The higher the power, the higher the chance of the study to be without a Type II error. Power is a measurement of the chance of a study to accept the null hypothesis when it should be rejected. In other words, statistical power is the likelihood that the experiment will detect a treatment effect of a particular size or difference. The higher the power, the higher the chances of finding a treatment difference. In general, a power of 80 to 90 percent

is considered acceptable in most clinical studies and this means that 1 in 5 to 1 in 10 trials will fail to detect a difference when in fact there is one.

Confidence Intervals

Another important measurement in providing information about the statistical significance of a study is the confidence interval (CI). The CI provides information on the range of a particular difference in outcome between a treatment group and a placebo group at a certain statistical significance. It indicates the probability that the estimate lies within the range. Confidence intervals are useful in determining what values can be expected for the population in general as opposed to the smaller study sample. Confidence intervals provide information about the range of the result; the smaller CI is indicative of greater precision. For clinical studies, the larger the sample size the more confident we are that these results are indeed reliable and not due to chance alone.

INTERPRETING THE DATA

In clinical drug trials, different parameters may be calculated to estimate the effect a study drug provides. The following are commonly used measures to calculate risk and benefit from a treatment modality.

Event Rate

The event rate is the rate of a particular event in treatment groups or controls.

$$\text{Event Rate} = \frac{\text{events in group}}{\text{number of subjects in group}}$$

Relative Risk

Relative risk (RR) is the ratio of the incidence of an event occurring in the treatment group to the incidence of occurrence in the control group. An example of this is the effect of lidocaine on treating seriously ill patients with multifocal premature ventricular contractions and the subsequent incidence of ventricular fibrillation and death. Results of the study showed that of 250 patients in the treatment group, 99 died. This would be an event rate of 39.6 percent. In the control group of 290 patients, 128 patients developed ventricular fibrillation and died, giving an event rate in the control group of 44.1 percent. The relative risk ratio would therefore be 0.90.

$$\text{RR} = \frac{\text{event rate in treatment group}}{\text{event rate in control group}}$$

Relative Risk Reduction

The relative risk reduction (RRR) is the proportion in rates of bad events between experimental and control groups. In the above scenario this would be calculated as a 10.2 percent risk reduction using lidocaine when compared to the control group.

$$RRR = \frac{\text{event rate control} - \text{event rate treatment}}{\text{event rate control}} \times 100$$

Absolute Risk Reduction

Absolute risk reduction (ARR) can be defined as the difference between the incidence of an event in the treatment group and the incidence in the control group. This is calculated by subtracting the control risk reduction by the study drug risk reduction. In the example described above this would produce a 4.5 percent (44.1 percent minus 39.6 percent) absolute risk reduction.

$$ARR = \text{event rate control} - \text{event rate treatment}$$

Number Needed to Treat

A common method used to put these results into perspective is the number needed to treat (NNT). The NNT is the number of patients who need to be treated to achieve one additional favorable outcome. This calculation provides the reader with an easier interpretation of the results, one that can be compared to other treatment groups and treatment modalities. To calculate this number in our example, divide 1 by the absolute risk reduction (1/4.5 percent), resulting in an NNT of 22. This is the number of patients needed to treat during the study period before an effect may be realized. If the number is very large, it means that many people will need to be treated before anyone actually benefits from the treatment. This is important when the drug is very expensive or has a relatively high adverse side effect profile.

$$NNT = 1 / ARR$$

Table 1. Summary of Risk and Risk Reduction Results

Measure	Equal Effect	Improved Benefit	Decreased Benefit
RR	1	<1	>1
RRR	0	>0	<0
ARR	0	>0	<0

Source: Applied Drug Information, Applied Therapeutics, Inc.

META-ANALYSIS

A meta-analysis can be an excellent source of information about drug efficacy. Meta-analyses critically review research studies and statistically combine their data to help answer questions that are not answered (because of statistical power) by any one of the single studies. This type of review can be dynamic, adding data from new studies as they become available.

Meta-analyses provide information about a particular subject based on work done by other researchers and authors. They condense a large amount of information into one document. Readers of these reviews must analyze the documents just as carefully as they would an original article.

Meta-analyses may have numerous biases and methodological inconsistencies that the reader must evaluate closely to avoid being trapped by the conclusions and recommendations of the author. Different reviewers of articles on the same subject may come up with information that is entirely contradictory. Meta-analysis builds on previous studies and these studies may or may not have the correct sampling, randomization, study design, or statistics to reach a proper conclusion, or the article may not present all of the relevant information. Reader beware.

For example, a meta-analysis of calcium channel blockers concluded that there was a higher death rate for patients on the drug than among controls who were not taking the medication. This was a highly publicized study that resulted in thousands of patients being taken off their calcium channel blocker. A subsequent review of the methodology used in the meta-analysis showed that two studies in the meta-analysis were given too much weight, which caused the overall statistics to show that the drug was detrimental.

The Cochrane Collaboration has worked to provide rigorous guidelines on the review and acceptance of articles for use in a meta-analysis. This collaboration has had success in providing meta-analyses on many important subjects. The Cochrane Collaboration provides for the updating of all of its meta-analysis documents by adding new studies to each review as they become available.

COMMON PROBLEMS WITH CLINICAL TRIALS

Study patients are not representative of the population that will actually take the drug. Selecting patients from a limited section of the population will provide opportunity for errors in outcomes of the study. An example is a clinical study of an antipsychotic drug used only in hospitalized patients with schizophrenia. Even though the outcome of the study may be excellent, patients confined to a hospital are not representative of patients whom clinicians would see in the community. Results of such a study would have to be interpreted carefully and may not be applicable to most community settings.

The number of participants in the study is too small. This is a frequent problem in many studies and one that affects the overall significance of the study. A study showing the superiority of a drug over placebo using 25 subjects is of questionable value.

Patients are not randomized correctly to the study or to the treatment groups. Were patients given equal opportunity to be in the treatment group and the control groups? Was this truly randomized, for example, by the use of computer-generated random numbers?

Patients randomized to the study did not complete the study. If a substantial number of patients were not accounted for at the end of the study, why were they left out of the results and conclusions? Was it because of side effects of a drug, lack of response, improved response (and no longer felt it necessary to return)? Can any of the dropouts be attributed to death? These are important to find out in a study as they may change the conclusions significantly or the relevance for your particular setting.

The drug is tested only against placebo, not the standard drug in its class. This is a common fault in many studies, especially studies that are sponsored by drug manufacturers. This type of study provides only a minimal amount of useful information on actual effectiveness. New drugs need to be compared against other established drugs as well as against placebo.

A new drug is compared to a drug with poor performance in the past. There is little need to review an article that compares the study drug to a drug that is relatively ineffective or that is not commonly used. The results will have very limited value.

Study participants or investigators are not blinded. Blinding is sometimes not possible, but it is highly desirable in most clinical studies. Open label studies are subject to investigator and subject bias and may not be able to provide reliable results. When blinding is done it needs to be described in the article, and this is frequently not done.

Efficacy and safety are based on one dosage regimen and do not provide an opportunity to learn more from various doses. Dosages in most cases should have a multiple-dose component to look at the effects of a range of doses.

Drug studies use fixed doses to compare different drugs. When comparing different drugs the study should compare different dosages of all drugs involved. If this is not done, then manipulation of the results can be easily accomplished by studying nonequivalent doses of each drug.

Study funding is provided by a drug company for its own product. Drug companies provide funding for a large number of studies every year in order to produce the necessary evidence to get regulatory approval of new drugs and to show superiority over competitor drugs. There is always the possibility of introducing bias in any study when a pharmaceutical company is involved. A noteworthy bias is when pharmaceutical companies do not publish a study because it was found to be unfavorable concerning one of their drugs.

The study is not subject to an adequate peer-review process. Failure to subject the study to adequate peer review may occur frequently, often by publishing in a “throwaway” journal that is not peer reviewed or via symposium proceedings. Drug companies often use these avenues to provide information affirming their drugs’ efficacy or safety. These types of publications must always be read with a close attention to study methodology and results.

The data presentation and analysis are misleading. Published data can be represented in different ways by reporting only the information that the investigators see as useful to their particular interest. Information taken out of context can make a particular drug look more promising than it really is. Reading the entire study in detail may provide an entirely different perspective.

Statistical significance of a trial is valid, but clinical significance is weak. It may be reasonable to prove statistical significance, but does this translate into anything that is reasonable to use in the health care system? A study that has shown an antilipemic drug to lower cholesterol by 5 percent may be statistically significant because of the large number of patients used in the trial. This 5 percent decrease will have little effect clinically and does not compare favorably with other antilipemic drugs that typically reduce cholesterol levels by 20 to 40 percent.

Confounding variables have not been controlled rigorously and results of the study may be due to the confounding variables. Two antidepressants for treating mild depression were shown to be equally effective. When further analysis was performed it was found that one group had a high percentage of subjects involved in group walking and exercising classes. This confounding variable could have a significant effect on the actual outcomes of the treatment group that it predominated in.

Bias introduced by the researcher may be difficult to assess, but may have an extremely important effect on the overall study. Bias can be introduced at many points in a clinical study. The bias that exists in most researchers is simply the need to succeed and accomplish the planned clinical study. Subconsciously or purposely, the investigator may manipulate the study if it is not controlled and blinded carefully.

Conclusions do not agree with results. This can happen because the investigator is not aware of the appropriate conclusions or has a particular bias to prove another point of view.

EVALUATING AN ARTICLE—THE USE OF A CHECKLIST

Evaluating the clinical literature is difficult. As we have seen in this session, you cannot necessarily rely on the conclusions and recommendations of the authors of clinical studies and other literature.

The actual review of an article requires having the skills, time, interest, and organization to accomplish the review. One method of improving the review process is using a checklist to organize the process. Checklists abound in the literature and the following information was abstracted from articles and texts listed in the key readings.

Checklist for Reviewing an Article

- What was the study design?

- Were both inclusion and exclusion criteria specified?
- Were subjects representative of the target populations?
- Were control subjects appropriate?
- Was the assignment of patients randomized?
- Was enough information provided to determine whether sample size was sufficient?
- Was power (sample size) discussed?
- If blinding of investigators and/or subjects to intervention was possible, was it done?
- Were attrition of subjects and reasons for attrition recorded?
- For those subjects who completed the study, were results completely recorded?
- Were known confounders accounted for by design or by analysis (e.g., randomized control trial)?
- Were the populations for which conclusions were drawn represented by the subjects in the study?
- Were clinically important outcomes considered?
- Are the likely benefits worth the potential harms and costs?
- Can the results be applied to your patients?
- Did the study reach statistical significance?
- Did the study reach clinical significance?
- Who was the sponsor of the study?

There are different methods to analyze an article and there is no single best way to accomplish this task. A systematic approach as presented here will provide guidance for the analysis.

Checklist for Reviewing a Meta-Analysis

- Does the meta-analysis answer the clinical question?
- What criteria did the authors use to find the articles?

- Do the authors clearly define both inclusion and exclusion criteria?
- Do the authors explain in detail how they obtained the relevant studies?
- Which database did they use for their search?
- Did the authors contact the original investigators?
- Have they included any unpublished studies in their meta-analysis?
- Does the meta-analysis provide a detailed description of how the studies were appraised?
- Who published the information and what kind of reputation does the publisher have?
- What is the date of the meta-analysis and what are the dates of the articles involved in the analysis?

Evaluating Other Drug Information Resources

The evaluation of other drug information resources is important and often neglected by busy practitioners. Before information is used from texts, newsletters, abstracting services, or consensus documents, there needs to be a general evaluation of the source (authors, editors, references) to ensure that it is providing unbiased and accurate information.

When reviewing these sources it is important to look at the reputation of the authors and publishers and any sponsors of these materials. Has the information been peer reviewed? How current is the information? Are references cited and are they important? Since these sources generally have a significant lag time to publication, what is the date of preparation and publication?

ACTIVITIES

For activities in this session, the participants will break up into groups of five individuals. A leader will be selected who will facilitate the discussion within the group. Active discussion within the groups is encouraged.

Activity 1. Evaluating a New Antimicrobial

Your DTC is considering the formulary addition of a new antimicrobial drug for treating lower respiratory tract infections in children. The drug study abstract you have just read concludes that this drug's efficacy is equal to a combination of antibiotics in treating pneumonia in hospitalized children.

This study looked at 35 children in the treatment group and 43 in the control group. The setting was a large university hospital. This was an open label study, and children receiving a new antimicrobial were compared with other children in the hospital who were receiving different antibiotic combination regimens to treat pneumonia. Patients were chosen to receive this antibiotic by the physician depending on the severity of the pneumonia. The drug requested for the formulary was typically given to children with less severe pneumonia (based on the judgment of the physician) while the combination drug therapy was reserved for children who appeared to be sicker and at higher risk.

Results showed that the study drug was equally effective as a combination of antibiotics and was less costly. There was no difference in the incidence of adverse drug reactions. The manufacturer of the drug sponsored the study.

You are especially interested in such a drug since it is less costly and the study shows that it is effective. Safety information is limited at the early stages of its marketing.

- How would you describe the study design? Is it valid?
- What are the controls in the study?
- How are patients randomized?
- What kinds of bias can be introduced in this type of study?
- Are the results of this study usable in your country?

Activity 2. Helsinki Heart Study

Subjects: 4,081 asymptomatic men aged 40–55 with dyslipidemia (total cholesterol minus HDL > 5.2 mmole/L)

Treatment: gemfibrozil 600mg twice daily (2,051 men) or matched placebo (2,030 men) in a five-year randomized double-blind study

Results: number of events (fatal, nonfatal myocardial infarction, or cardiac death)

Gemfibrozil—56 events
Placebo—84 events

Please calculate the following:

- Event rate for placebo group (%)—

- Event rate for active drug group (%)—

- Relative risk—

- Relative risk reduction (%)—

- Absolute risk reduction (%)—

- Number needed to treat for five years to prevent one event (NNT)—

Activity 3. Article Review

See the attached articles on trimethoprim/sulfamethoxazole and angiotensin-converting enzyme inhibitors. Read and analyze the articles for the following:

- Study design
- Sampling
- Randomization
- Controls
- Blinding
- Results
- Conclusions

SUMMARY

Evaluation of the primary, secondary, and tertiary literature is an important element in the process of selecting drugs. A careful evaluation of the literature is important as information resources can contain biased, inaccurate, and incomplete information. The most important factors for evaluating the clinical literature include—

- Sampling
- Randomization
- Control groups
- Blinding techniques
- Potential bias and confounding factors
- Methodology
- Data analysis
- Results
- Conclusions

Careful examination of the primary literature will bring new insight into the accuracy of the conclusions stated by the authors of the articles. Just as important is the careful analysis of the secondary and tertiary literature to obtain unbiased and accurate information from these sources. The trained and experienced reader will be able to provide the DTC with valuable information about any new drug being proposed for the formulary.